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Synthesis of 4,5-dihydroimidazole-2-carboxamides

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Abstract: A convenient procedure was developed for the preparation of 4,5-dihydroimidazole-2-carboxamides by the reaction of monothiooxamides with ethylenediamine.

Keywords: Monothiooxamides, 4,5-dihydroimidazole-2-carboxamides, ethylenediamine, amines.

Introduction

Results and Discussion

Experimental Part

References

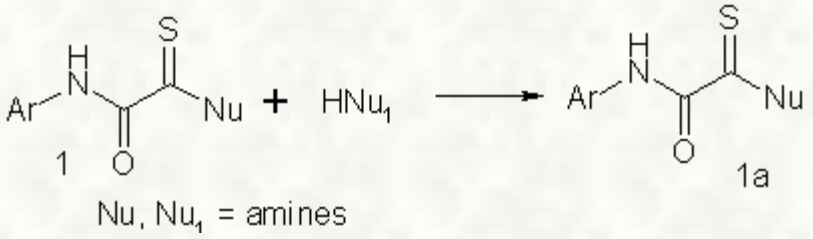
Introduction

4,5-Dihydroimidazole derivatives find application as corrosion inhibitors[1, 2] and as starting compounds in the synthesis of biologically active compounds, for example, 4,5-dihydroimidazole-2-carboxamides, possessing anti-hypertensive properties.[3]

Previously, we have developed a simple approach to the synthesis of monothiooxamides[4] by the reactions of chloroacetamides with a solution of elemental sulfur in amines (prepared in advance) at room temperature. In this work, we studied the reactions of monothiooxamides with N-nucleophiles to develop a simple convenient procedure for the preparation of 4,5-dihydroimidazole-2-carboxamides under mild conditions.

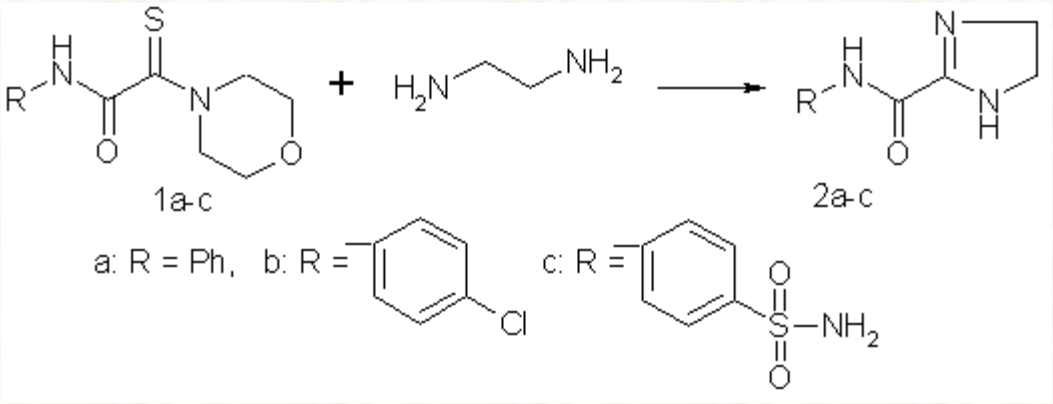
Results and Discussion

It is known[5] that the reactions of primary amines with thioamides can either proceed with the formation of an imine fragment or result in transamidation. With the aim of examining general regularities of reactions of monothiooxamides with amines, we first studied the reactions of N(O)-phenylmonothiooxamides (1) with primary amines.

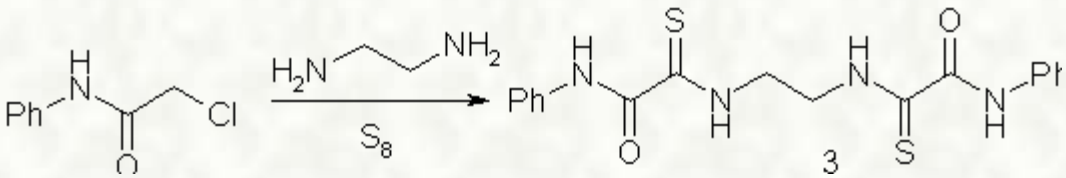


It was found that transamidation did not affect the C=S group and the amino group of the amide fragment. The highest yield of compound (1a) was obtained in the reaction with N(S)-morpholino deriva&#65533;tives of monothiooxamides, which can be obtained from chloroacetamides in high yields.[4] The electron-acceptor and electron-donor substituents in the benzene ring of the amide fragment have no noticeable effect on transamidation under the action of primary amines.

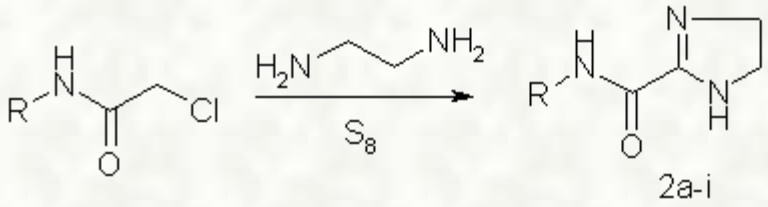
With the aim of synthesizing 4,5-dihydroimidazole-2-carboxamides, we studied the reactions of N(S)-morpholino derivatives (1a-c) with ethylenediamine. The reactions were carried out in ethylene&#65533;diamine or DMF at ~20 &#65533;C. 4,5-Dihydroimidazole-2-carboxamides (2a-c) were prepared in 60&#65533;90% yields.



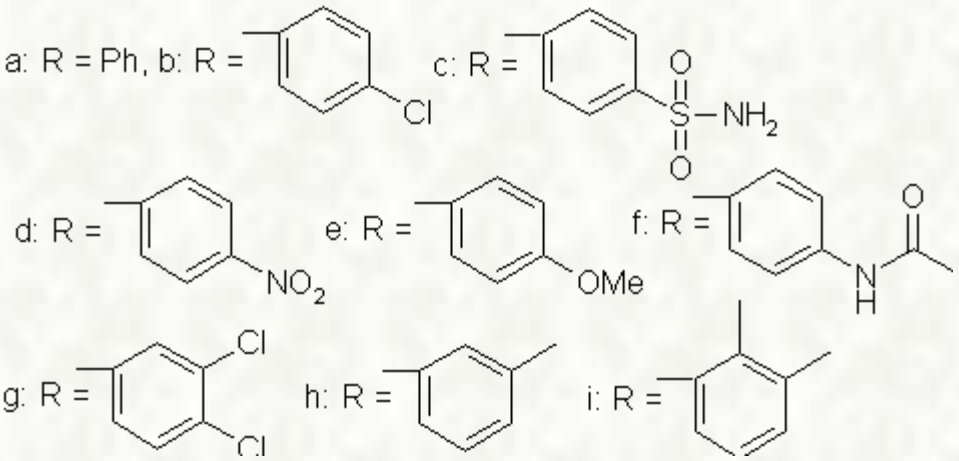
Based on the results of transamidation of monothiooxamides, it can be concluded that the first stage of the reaction with ethylenediamine involves the replacement of the morpholine fragment to form the corresponding monothiooxamide. We examined the pos&#65533;sibility of the synthesis of 4,5-dihydroimidazole-2-carboxamides in one stage by the reaction of chloroacetanilides with a solution (prepared preliminar&#65533;ily) of elemental sulfur in ethylenediamine. It appeared that the direction of the reaction depended on the order in which the reagents were introduced into the reaction. When a solution of elemental sulfur in ethylenediamine was added to chloroacetanilide, bis(thiooxamide) (3) was formed.



When chloroacetanilide was added to a solution of sulfur in ethylenediamine, the corresponding 4,5-dihydroimidazole-2-carboxamides (2a-i) were obtained in 50–80% yields.



2a-i



Thus, we developed a simple procedure for the synthesis of 4,5-dihydroimidazole-2-carboxamides from readily available reagents.

Experimental

The IR spectra were recorded on a Specord IR-80 spectro-photometer in KBr pellets. The H^1 NMR spectra were obtained on Bruker AC-200 (200 MHz) and Bruker WM-250 (250 MHz) instruments in DMSO-d_6 relative to HMDS. The mass spectra were measured on a Varian MAT CH-6 instrument with direct inlet of the sample into the ion source with a control voltage of 1.75 kV; the energy of ionizing electrons was 70 eV. The melting points were measured on a Boetius table and are uncorrected. The reaction mixtures were analyzed and the purity of the products isolated was monitored by TLC on Silufol UV-254 plates in an EtOAc–hexane system (1:1, v/v).

Reactions of N(O)-arylmonotbiooxamides with primary amines (general procedure). N(O)-Arylmonothiooxamide (0.10 g) was dissolved in the corresponding amine (1 ml). The solution was kept at room temperature until the initial compound disappeared (TLC control) and then poured into water (20 ml). The precipitate that formed was filtered off, washed with water, dried, and recrystajlized from ethanol.

Reactions of N(O)-arylmonothiooxamides with ethyienediamine.

N2-phenyl-4,5-dihydro-1H-2-imidazolecarboxamide (2a). A solution of S-morpholino-N(O)-phenylmonothiooxamide (0.10 g, 0.4 mmol) in ethylenediamine (1 ml, 15 mmol) was kept for 1.5 h at room temperature. Then the reaction mixture was poured into water and the precipitate that formed was filtered off and dried. After recrystallization from ethanol, the yield of compound 2a was 0.23 g (60%), m.p. 195-196 °C.

N2-(4-chlorophenyl)-4,5-dihydro-1H-2-imidazolecarboxamide (2b). The reaction with monothiooxamide was carried out analogously. The yield of compound 2b was 0.07 g (90%), m.p. 235–236.5 °C (from ethanol).

N2-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-2-imidazolecarboxamide (2c). A solution of monothiooxamide (0.10 g, 0.3 mmol) in ethylenediamine (2.0 ml, 1.79 g, 29 mmol) was kept for 2 h at room temperature (TLC control, EtOAc–hexane, 3 : 1). The reaction solution was poured into water (50 ml) and extracted with EtOAc (3?30 ml). The organic layer was dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was crystallized from ethanol. The yield was 0.05 g (63%), m.p. 280 °C.

Reactions of chloroacetamides with ethyienediamine and elemental sulfur (general procedure for the preparation of 4,5-dihydroimidazole-2-carboxamides). A mixture of sulfur (1-0 g, 30 mmol) and ethylenediamine (10 mL, 150 mmol) was stirred for 30 min at room temperature until the dark-red solution was formed. Then chloroacetanilide (6 mmol) was added portionwise with stirring over 10 min. The reaction mixture was stirred for 30 min and poured into water (100 mL). The precipitate was filtered off, washed with water, dried, dissolved in acetone, and filtered to remove unconsumed sulfur. The acetone solution was concentrated and the residue was recrystallized from ethanol. The characteristics of the resulting 4,5-dihydroimidazole-2-carboxamides 2a-i are given in Table1.

N,N′-Bis(2-anilino-2-oxothioacetyl)-l,2-ethylenediamine (3). A mixture of sulfur (0.5 g, 15.6 mmol) and ethylenediamine (0.2 ml, 0.18 g, 2.9 mmol) was stirred for 30 min at room temperature. Then the reaction mixture was added portionwise to a solution of chloroacetamide (0.5 g, 2.95 mmol) in DMF (5 ml) over 10 min. After 30 min (TLC control), the mixture was poured into water (50 mL). After 12 h, the precipitate that formed was filtered off, dried, dissolved in acetone, and filtered to remove unconsumed sulfur. The acetone solution was concentrated and the residue was recrystallized from ethanol. The yield was 0.40 g (36%), m.p. 198-200 °C. Found (%): C, 56.10;

H, 4.39; N, 14.37. $C_{18}H_{18}N_4O_2S_2$. Calculated (%): C, 55.94;

H, 4.69; N, 14.50. H^1 NMR, d: 3.98 (m, 4 H. 2 -??-);

7.25 (t, 2 H, 2 H arom.); 7.37 (t, 4 H, 4 H arom.); 7.75 (d, 4 H, 4 H arom.); 10.30 (s, 2 H, 2 NH); 11.00 (s, 2 H, 2 NH). MS, *m/z:* 386 [M]*

Table 1

Table 1. Characteristics of the synthesized 4,5-dihydroimidazole-2-carboxamides (2a–i)

Compound	Yield (%)	M.p./°C	Found / Calculated (%) C	H	N	Molecular formula	^{1}H NMR (DMSO-d_6), δ	MS, m/z
2a	72	195–196	63.32 63.48	5.95 5.86	22.41 22.21	$C_{10}H_{11}N_3O$	3.75 (s, 4 H, 2 $-CH_2-$); 7.05 (t, 1 H, H arom.); 7.30 (t, 2 H, H arom.); 7.57 (d, 2 H, H arom.)	188 $[M-1]^+$
2b*	80	236–238	53.51 53.70	4.40 4.51	18.83 18.79	$C_{10}H_{10}ClN_3O$	3.65 (s, 4 H, 2 $-CH_2-$); 7.35 (d, 2 H, H arom.); 7.80 (d, 2 H, H arom.); 10.40 (s, 1 H, NH)	223, 225 $[M]^+$
2c	63	280–281	44.81 44.77	4.38 4.51	20.79 20.88	$C_{10}H_{12}N_4O_3S$	3.60 (s, 4 H, 2 $-CH_2-$); 4.0 (br.s, 4 H, NH); 7.75 (d, 2 H, H arom.); 7.95 (d, 2 H, H arom.)	267 $[M-1]^+$
2d	50	274–276	51.40 51.28	4.35 4.30	23.80 23.92	$C_{10}H_{10}N_4O_3$	3.25 (br.s, NH); 3.65 (s, 4 H, 2 $-CH_2-$); 8.05 (d, 2 H, H arom.); 8.25 (d, 2 H, H arom.)	234 $[M]^+$
2e	75	199–200	60.10 60.26	5.88 5.98	19.33 19.16	$C_{11}H_{13}N_3O_2$	3.25 (br.s, NH); 3.65 (s, 4 H, 2 $-CH_2-$); 3.73 (s, 3 H, $-OMe$); 6.90 (d, 2 H, H arom.); 7.65 (d, 2 H, H arom.)	219 $[M]^+$
2f	78	278–280	58.61 58.53	5.49 5.73	22.60 22.75	$C_{12}H_{14}N_4O_3$	2.00 (s, 3 H, Me); 3.65 (s, 4 H, 2 CH_2-); 7.10 (s, 1 H, NH); 7.50 (d, 2 H, H arom.); 7.65 (d, 2 H, H arom.); 9.90 (s, 1 H, NH); 10.20 (s, 1 H, NH)	246 $[M]^+$
2g**	52	185–186	46.85 46.54	3.49 3.51	16.29 16.28	$C_{10}H_9Cl_2N_3O$	3.25–3.40 (br.s, NH); 3.65 (s, 4 H, 2 $-CH_2-$); 7.55 (d, 1 H, H arom.); 7.75 (d, 1 H, H arom.); 8.10 (s, 1 H, H arom.)	257, 259 $[M]^+$
2h	65	120–122	65.10 65.01	6.36 6.45	20.53 20.68	$C_{11}H_{13}N_3O$	2.25 (s, 3 H, Me); 3.30 (br.s, NH); 3.63 (s, 4 H, 2 $-CH_2-$); 6.90 (d, 1 H, H arom.); 7.19 (t, 1 H, H arom.); 7.55 (t, 2 H, H arom.)	203 $[M]^+$
2i	74	158–161	66.43 66.34	6.98 6.96	19.28 19.34	$C_{12}H_{15}N_3O$	2.05 (s, 3 H, Me); 2.25 (s, 3 H, Me); 3.25 (br.s, NH); 3.65 (s, 4 H, 2 $-CH_2-$); 7.05 (m, 2 H, H arom.); 7.30 (d, 1 H, H arom.)	217 $[M]^+$

* Found (%): Cl, 15.73. Calculated (%): Cl, 15.85.
** Found (%): Cl, 27.55. Calculated (%): Cl, 27.47.

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